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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/743,347	KORNELUK ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-77,79,80,82-87,89-92,94,95,97 and 99-133* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-77,79,80,82-87,89-92,94,95,97,99-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response, filed 06/06/05, canceling claims 1-68, 78, 81, 88, 93, 96, 98, amending claims 69-77, 79-80, 82-87, 89-92, 94-95, 97, 99-101, 103 and adding new claims 104-133. Therefore, claims 69-77, 79-80, 82-87, 89-92, 94-95, 97, 99-133 are currently pending in this application[1].

All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections repeated herein. Since any new ground of rejection is necessitated by material changes to the claims, **this action is made FINAL.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 69-77, 79-80, 82-87, 89-92, 94-95, 97 and 99-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

This is a new ground of rejection necessitated by amendment to the claims. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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[1] Applicant refers to the cancelled claims as still pending (Remarks, p. 13), but presumably this is an error and the claim set is controlling regarding this issue.

More particularly, all independent claims (i.e., claims 69, 86 and 104) recite the limitation "of a length of up to 299 bases" which does not find support in the instant disclosure. A review of the specification, including portions to which Applicant refers in Remarks, filed 06/06/2005 (Specification, p. 12, line 26, to page 13, line 7; page 17, lines 20-22; page 30, line 19; page 31, lines 6-9), reveals that said limitation lacks sufficient support. It is noted that SEQ ID NO: 2 is 299 nucleotides in length, but this does not provide support for setting an upper limit of 299 bases, because the specification teaches to the contrary. For example, the specification explicitly teaches that a 500 nucleotide region 5' to 3' can encode the XIAP IRES. (Specification, p. 3, ll. 14-17; describing the first aspect of the invention). Further, in describing the seventh aspect of the invention (i.e., antisense nuclei acid molecules) the specification teaches that antisense molecules may be complementary to nucleotide sequences of the nucleic acid of the first aspect of the invention (i.e., 500 nucleotide region of XIAP IRES).

"[T]he introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph". See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Indeed, the specification recites that the antisense molecules can be "even as long as a full-length IRES". (e.g., p. 10, l. 2). Thus, the specification actually provides implicit support for an antisense molecule that is more than 299 bases in length, contrary to what is claimed. As such, **the limitation "up to 299 bases" constitutes impermissible New Matter**.

2. **Claims 69-77, 79-80, 82-87, 89-92, 94-95, 97 and 99-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

This rejection is of record and is new only insofar as it is applied to the new claims. The rejection is repeated herein with modification to address amendments to the claims. A response to Applicant's argument is set forth immediately following the body of this rejection. (Infra, Response to Arguments).

The claims are drawn to antisense molecules comprising a base sequence that target portions of any X-linked Inhibitor of Apoptosis Internal Ribosome Entry Site (XIAP IRES) transcript or gene. Specific embodiments are drawn to the particular sequence stretches that are *no more than 299 bases* and that are complementary to the target nucleic acid molecule for *human* XIAP IRES, or *SEQ ID NO: 2* (italics denote the salient amendment to the claims). More particular embodiments are directed to the antisense molecule as containing at least 10, 14, 25 or 40 consecutive nucleotides relative to SEQ ID NO: 2. Thus, as to dependent claims the genus of antisense molecules is delimited to 10, 14, 25 or 40 consecutive nucleotides within the 299 nucleotides of SEQ ID NO: 2. However, at the most stringent level (i.e., subgenus of 40 consecutive nucleotides) there are over 250 different embodiments that are encompassed in the subgenus (thus the subgenus of 25, 14 and 10 consecutive nucleotides relative to SEQ ID NO: 2 would each respectively encompass progressively larger numbers of additional embodiments). The claims encompass over 1,100 different antisense structures, wherein one of skill would have to envisage which of the 1,100 structures would correspond to the requisite functionality of inhibiting transcription or translation of XIAP in any cell.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The specification discloses two XIAP IRES having the sequences in accordance to SEQ ID NOs: 1 and 2 (murine and human respectively; as shown in Figure 5). The examples provided are directed to mutational analysis of the IRES element. Thus, as a matter of fact, there are actually no examples disclosed of antisense molecules that are shown to inhibit translation transcription in a cell. As stated above, the claims read on a broad genus of antisense DNA or RNA molecules targeting transcription or translation of XIAP IRES in any cell. The vast genus would encompass an enormous number of different structures, for which a common or equivalent structure is not identified relative to the required function of inhibiting XIAP transcription or translation; in this regard there is an omission in the instant disclosure, which omission is not ameliorated by evidence in the art.

For example, a single nucleotide change in a target sequence could determine whether an antisense molecule binds the target sequence to function as antisense (e.g., inhibit translation). Because the antisense molecule is directly defined by the target molecule sequence, one of skill could not envisage all members of the genus as defined by any XIAP IRES, thus could not identify all the antisense molecules as claimed. Such variability is due to mRNA secondary structures, which in turn determine if the antisense molecule indeed functions as an antisense

molecule. Put another way, the target sequence determines target structure, which determines whether a complementary sequence functions as an antisense molecule. (See, Branch, AG, TIBS. 1998; 45-50; p. 49, col. 1; indicating that of nearly two thousand antisense molecules screened for a known target sequence that only a handful bound stably to the mRNA due to accessibility of mRNA substructures that form). Therefore, variants for a particular XIAP IRES sequence can themselves form a separate genus of target molecules that define the antisense molecules. For example, a single base change within a target sequence can affect the free energy of a given secondary structure, which would determine whether stem loop structures form, thus providing regions that are accessible for hybridization. (See, Galderisi et al. J. Cell. Phys. 1999; 181:251-257, at p. 252, col. 1).

Therefore, the claims are drawn to an enormous scope of different structures, which are prone to high variability due to slight changes in their nucleotide sequences. It would be evident that the ability of a given antisense molecule to inhibit translation by binding a XIAP IRES would have to be determined empirically, because inhibition of translation/transcription cannot be predicated by simple complementary base pairing. In other words, one antisense molecule is not necessarily equivalent to another for a given target sequence, in functioning to inhibit translation/transcription. Moreover, it is important to note that antisense molecules that target mRNA are not necessarily interchangeable or equivalents in inhibiting transcription, i.e. targeting DNA (e.g. triplex formation). Indeed, relative to mRNA targeting, there is even less known about structure to function correlation for triplex formation to prevent transcription. However, similar to mRNA targeting triplex formation is affected by single base variants in the duplex target DNA, which affect the stability of the triplex formation. (See, Crooke, ST.

Antisense Research and Application. 1998 New York, Springer; pp. 569-574). In addition, design and construction triplex forming antisense molecules is constrained by the fact that such molecules are limited to hybridization with purine bases composing polypurine-polypyrimidine tracks within the target DNA. (Jen et al. Stem Cells. 2000; 18:307-19; p. 308, col. 1 bridging ¶ to col. 2). "The targeting efficiency of TFOs [triplex forming oligos] is further constrained by...[the] need for divalent cations...[and most importantly] access to DNA compacted within the chromosome structure." (Id.). Therefore, simply disclosing a sequence that encompasses an XIAP IRES would not necessarily allow one of skill to envisage the antisense molecule structures that can function to inhibit transcription by binding DNA in the nucleus.

Given the enormous breadth of the antisense molecules encompassed by the rejected claims, and given the limited description from the instant specification of such molecules, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to describe the broadly claimed genus of antisense molecules targeted to any XIAP IRES from any source. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Therefore the general knowledge and level of skill in the art do not supplement the omitted description for a sufficient representative number of XIAP IRES structures. Since the disclosure fails to describe common attributes or characteristics that identify the members of the genus and because the genus is highly variable, the disclosed sequences of SEQ ID NO: 2 are not deemed sufficient to describe the claimed genus. (See MPEP § 2163; indicating that a sequence

described by functional characteristics, without any known/disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic to fulfill the written description requirement, even when accompanied by a method of obtaining the claimed sequence).

Response to Arguments

Applicant's arguments filed 06/06/2005 have been fully considered but they are not persuasive. It appears Applicant's only argument is that the amendments to claims 69 and 86 (as also embodied by new claim 104) obviate the rejection. The amendments result in a smaller genus of nucleic acid molecules, in that the antisense molecules have an upper limit of 299 bases. However, as stated herein above, the genus of nucleic acid molecules includes over 1,100 different embodiments, for which the specification does not provide a single identified structure that corresponds to the requisite functionality of inhibiting transcription or translation of XIAP.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("The description must clearly allow persons of ordinary skill in the art to recognize that (the inventor) invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious" and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

The instant description merely provides the potential targets for antisense inhibition, but it does not describe or convey to the artisan that Applicants identified any of said antisense molecules to inhibit XIAP transcription or translation in any cell. Furthermore, the Guidelines for Written Description state, "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). Antisense technology is not a conventional or predictable art. (supra, Branch, 1998; Galderisi, 1999; Crooke, 1998; see also, "State of the Art...", Enablement Rejection, infra). Against such a backdrop a disclosure, that merely identifies targets to which over 1,100 antisense molecules may bind and function to inhibit transcription or translation, does not meet the written description requirement, because the artisan cannot envisage a sufficient number of antisense molecules that correspond to the requisite functionality.

Indeed, for inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable, which are known to one of ordinary skill in the art, more evidence is required to show possession. For example, disclosure of only a method of making the invention and the function may not be sufficient to support a product claim. See, e.g., *Fiers v. Revel*, 984 F.2d 1164, 1169, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993); *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). Moreover, in such instances the alleged conception fails the written description requirement not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that

undermines the specificity of the inventor' s idea of the invention. *Burroughs Wellcome Co. v. Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994).

In view of the foregoing, notwithstanding the narrowing amendments, the genus of antisense molecules is not adequately described. Therefore, the rejection is maintained.

3. **Claims 99-103, 121-125 and 129-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.**

This rejection is of record and repeated herein with some modification to address material changes to the claims. The rejection is new in its application to the new claims which are introduced by amendment. A response to Applicant's arguments are set forth immediately below. (Infra, Response to Arguments).

The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are enormously broad drawn to method of treating *any* cancer in *any* cell/tissue in *any* subject using antisense molecules that target either

mRNA or DNA that represents any XIAP IRES to inhibit transcription or translation of XIAP. Furthermore, the antisense molecules can be RNA or DNA and can be delivered by any means or mechanism into the cell cytoplasm/nucleus. As noted above in the Written Description rejection, the claims are narrower in the sense that the claimed genus encompasses fewer, but still a substantially large number of embodiments (i.e., over 1,100 antisense molecules).

Nature of the invention. Generally the invention is directed to antisense therapy. The claims are drawn to a method of treating *any* cancer in a subject using antisense molecules that inhibit transcription or translation, reducing XIAP levels in cells, thus increasing the cell's susceptibility to apoptosis. The antisense molecules are delivered into the cell cytoplasm or nucleus to effect binding to target sequences (i.e. XIAP IRESs). The methods and pharmaceutical compositions require *in vivo* applicability and the correlation between antisense compound hybridization to target sequences *in vivo* with the reduction of XIAP protein, thus directly resulting in apoptosis of cancerous cells.

State of the art/Unpredictability of the art. The state of the art for antisense therapy in humans is still developing with some progress. However, there are many more questions about antisense that remain to be answered, with limitations for such technology grounded in pharmacokinetic and toxicological properties. (See generally, Crooke, ST. Curr. Mol. Med. 2004; 4:465-87; p. 484, col. 2). For proof of mechanism, a number of factors are recommended including, dose response analysis, examination of different classes of oligonucleotides/antisense molecules, determination of potency, demonstration of proposed mechanism of action, evaluation of the therapeutics' specificity and evaluation of non-antisense effects. (Id., p. 466, col. 1).

Generally, the antisense molecules operate by either an RNase H-dependent degradation of the target mRNA or by positional antisense molecules that operate as steric-blockers that physically prevent or inhibit the progression of splicing or translational machinery (as in instant invention). Irrespective of the mechanism, antisense molecules must be delivered into cells, the precise mechanism for which is unclear. Delivery can be via naked oligonucleotides or through vectors, but "all clinical trials with antisense oligonucleotides are carried out with naked oligonucleotides." (Diaz et al. Mol. Cancer Therap. 2002; 1: 347-55; p. 351, col. 2, ¶ 2).

The art of antisense therapy of cancer is unpredictable in many respects. For example, a variety of factors can affect the behavior of antisense molecules *in vivo*, including oligonucleotide purity, structural modifications, target RNA structure and substructure, variability in cellular uptake and differential tissue- or organ-distribution, non-target binding, degradation before delivery or binding and metabolism of antisense molecules *in vivo*. (See supra, Crooke, 1998; pp. 3-7). One of the major problems in targeting mRNA is that within cells the transcripts exist in secondary structures and substructures that maybe further dominated by interactions with cytoplasm proteins. As such, the actual target sequences for a given antisense molecule may actually be inaccessible, thus leading to the requirement for much empirical data. In this regard, computer programs that generate three-dimensional folding patterns based on free energy calculations often provide results with no meaningful *in vivo* relevance. (Supra, Jen et al. 2000; p. 313, col. 1, ¶ 3). Therefore, simply knowing the sequence for a particular mRNA is not enough.

Non-target affects are particularly salient in evaluating unpredictability, indeed, "the antisense field has been turned on its head by the discovery of non-antisense effects, which occur

when a nucleic acid drug acts on some molecule other than its intended target – often through entirely unexpected mechanisms." (See supra, Branch, 1998; p. 45, col. 2). Such non-antisense effects include the antisense molecules binding non-target proteins with unexpected and unpredictable outcomes, such as affecting housekeeping genes and related proteins. (See supra, Crooke, 1998; pp. 3, 13, 277). In addition, there is unpredictability with respect to the particular antisense molecules toxicity *in vivo*, which may be independent or dependent on the particular sequence. For example, either the native or modified antisense molecule can cause immune activation, which can in turn be dependent on the antisense molecule concentration or length. (Id., p. 243). One such immune reactivity is activation of tumor necrosis factor, which can actually lead to tumor death, but not through any antisense binding mechanism. (Id.). Antisense molecules have also been shown to activate SP1 transcription factor, thus affecting cell proliferation and differentiation. (e.g. Biroccio et al. Oncogene. 2003; 22:6579-88; p. 6579, col. 2). Toxicity can also involve hematological effects, such as anticoagulation, thrombocytopenia, anemia and complement activation. (Id., pp. 233-237).

It should be noted that even a single base difference between antisense molecules deems inappropriate any direct correlation between results obtained for an XIAP from one particular source (e.g. murine) as compared to another (e.g. human) with respect to predictability of toxicity. (e.g. Hu et al. Clin. Cancer Res. 2003; 9:2826-36; p. 2835, top). As pointed out previously, a major limitation for antisense therapeutics is that delivery can be problematic. (e.g. Jen et al. Stem Cells. 2000; 18:307-19; p. 313, col. 2). For example, antisense molecules can be delivered into non-target genes and actually integrate, thus leading to mutagenesis. (Supra, Crooke, 1998; p. 27).

Although an integration event may be rare, it is merely one of a milieu of factors that figure into the unpredictability analysis. Another problem with delivery is that even *in vitro* there is great variation between different cell types with respect to antisense molecule internalization and uptake. (Supra, Galderisi et al. 1999; p. 252, col. 2). Moreover, "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man demonstrate[ing] that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies." (Crooke, 1998; p. 3). Pharmacokinetics and toxicity have broad and unpredictable implications in various animal models, such as simian and murine models. (e.g. Crooke, 2004; p. 469, col.1 bridging ¶ to col. 2; p. 471, col. 1 bridging ¶ to col. 2; pp. 481-2; for further discussion of toxicities related to antisense molecule treatment regimes).

In addition, the antisense molecules would have to be delivered to nearly every tumor cell in order to be effective..." (Curiel, DT. Breast Cancer Res. 2000; 2:45-49; p. 48, col. 1, ¶ 3). One reason for such comprehensive delivery is that target genes in cancer cells (e.g. XIAP) are often over-expressed, thus require high-level inhibition. Furthermore, "considering the multitude of molecular entities and signaling pathways that regulate the proliferation and the life/death decision in cancer cells, inhibition of a single target gene is not sufficient to suppress tumor growth." (Supra, Biroccio et al. 2003; p. 6585, col. 2, last ¶).

In sum, antisense therapeutics must overcome several obstacles for *in vivo* application whether in inhibiting translation or transcription, where the obstacles include attaining stable intracellular levels and cell delivery, the requirement for evaluation of extensive empirical data,

target mRNA structure, accessibility predictions and the lack of computer model *in vivo* relevance, non-antisense effects, toxicity, and the lack of correlation between *in vitro* results and *in vivo* application.

Amount of guidance provided. There is no substantial relevant guidance provided. There is some prophetic and generic guidance provided on how antisense therapeutics can be used to target gene expression. (e.g. Spec., pp. 31-32). The disclosure is actually directed to characterization of untranslated upstream XIAP sequences from human and comparison with murine, including *in vitro* data on reporter assays/cells. Significantly, there is actually no guidance provided as to *in vivo* application of antisense molecules to treat cancer through apoptosis involvement. Therefore, the specification as filed, does not describe an *in vivo* method of inhibiting XIAP expression in cancer cells so as to promote apoptosis, either through inhibition of XIAP translation or transcription.

Number of working examples. There are no relevant working examples provided for *in vivo* therapy of cancer. All the *in vitro* data provided involves vectors and cells containing the vectors, which are used to characterize the human XIAP upstream region so as to identify potential IRES sequences, and significantly, are not examples of antisense molecules or antisense inhibition of XIAP transcription or translation.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. However, given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art, the lack of relevant guidance in the instantly filed specification and lack of relevant working examples, it must be considered that the skilled

artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention.

Response to Arguments

Applicant's arguments filed 06/06/2005 have been fully considered but they are not persuasive. Applicant argues that the narrowing amendments substantially reduce the amount of experimentation that would be required and that the post filing publication of U.S. Application No. 10/400,382[2] (Publication No. 2003/0190659; hereinafter '659 application) provides enabling support for the instant claims.

The publication date for the '659 application is October 2003, which is nearly 4 years after the effective filing date of the instant application. Therefore, the disclosure therein would not have been available to one of skill in the art at the time invention for the instant invention. Furthermore, the '659 application's disclosure is not incorporated into the instant application. Even if there were a reference as such, mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973). See MPEP § 608.01(p). In addition, *arguendo* if the '659 disclosure were incorporated into the instant disclosure, identification of 10 species within the instantly claimed genus would not likely enable the full scope of the instant claims. In any event, whether the '659 disclosure is enabling is rendered moot, because for the incorporation by reference to be effective as a proper safeguard, the incorporation by reference statement must be filed before or at the time of filing of the later-filed application.

[2] Common assignee with instant application.

An incorporation by reference statement added after an application's filing date is not effective because **no new matter can be added to an application after its filing date**. (See, 35 U.S.C. 132(a)).

Thus, the only remaining issue is whether the narrowing amendments to the instant claims correspond to an enabling disclosure in the instant application. As noted above in the Written Description rejection, while the genus of antisense molecules encompasses fewer embodiments, the number of embodiments is still relatively large, given the unpredictability and the state of the art. Thus, the claims are still broad in the number of potentially nonenabled embodiments. The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). In the instant case, the antisense molecules are nothing more than prophetic examples that *may potentially* inhibit XIAP transcription or translation in some cell/tissue/subject. But given the many grounds of unpredictability, even to make/use certain antisense molecules within the claimed genus would require substantial and undue experimentation. (supra, State of Art/Unpredictability of the Art; discussing obstacles in antisense therapy, which include targeting, unintended targeting, delivery, toxicity/non-target effects, degradation, cellular uptake, accessibility of target molecules, immune reactivity, etc.)

The instant disclosure does not provide guidance or address any of such obstacles. Therefore, it is of little moment that the genus of antisense molecules has been narrowed to over 1000 versus tens of thousands, because the same underlying factors for unpredictability still remain, and such factors are not accounted for in the instant disclosure. Indeed, there is not a single example of an antisense molecule that is administered or introduced into a cell *in vitro* or *in vivo*.

It should be made clear that, the enabling specification must teach those skilled in the art to make and use the *full scope* of the claimed invention without undue experimentation. "Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404; *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification)." *In re Wright* (CAFC) 27 USPQ2d 1510 at 1513. In instant, the claims encompass treatment of any cancer in any cell in any subject utilizing any of over 1,100 antisense molecules to inhibit transcription or translation of XIAP. However, the disclosure does not teach how to use a single antisense molecule *in vivo* or *in vitro*.

In view of the foregoing and for reasons of record, it is believe that there is ample support provided to show that the instant disclosure is not enabling. The basis for the rejection is grounded in both the cited literature (e.g., cited in the body of both the Written Description and the Enablement rejections), which provides further support for the scientific reasoning provided.

In any event, *Ex parte Sudilovsky*, 21 USPQ2d 1702 (BPAI 1991) states, "[T]he *Marzocchi* decision clearly sanctions sound scientific reasoning as an acceptable alternative to patents and printed publications in support of an examiner's holding that a disclosure is not enabling". In sum, the instant disclosure does not teach how to make and use the invention. Thus, the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. **Claims 69-77, 79-80, 82-87, 89-92, 94-95, 97, 104-120, 125-128 and 133 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 9 of U.S. Patent No. 6,159,709 (hereinafter the '709 patent).**

This rejection is of record and repeated herein. The rejection is new in its administration to the new claims, which administration is necessitated by amendment. It is noted that Applicant requests this rejection be held in abeyance pending resolution of all other rejections. However, as other rejections are applied herein (i.e., the claims are not allowed), this rejection is maintained.

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are drawn to particular antisense molecules that contain base sequences with complementary sequences to portions of the disclosed sequence structures (i.e., SEQ ID NO: 2, 5, 7, 21, 25, 27 and 29) with at least 10 consecutive nucleotides. Reference claims 8 and 9 are directed to antisense molecules having at least 10 consecutive nucleotides as directed to target sequences of SEQ ID NO: 2. Furthermore, the reference disclosure discloses SEQ ID Nos: 2, 5, 7, 21, 25, 27 and 29, as well as relating the sequences to the characterized XIAP IRES sequence (Figure 5 in both the instant and reference application, as the specifications are identical).

Therefore, instant claims cannot be considered patentably distinct from claims 8 and 9 of the '709 patent. One of ordinary skill in the art examining the '709 patent's claims would have been motivated to examine the full disclosure, including Fig. 5 and the corresponding sequence disclosure to fully understand the identity of the target sequences as related to the claimed antisense molecule.

It would have been obvious to one of ordinary skill in the art to modify the antisense molecules of the '709 patent consonant with the reference patent's disclosure of the full upstream sequence characterized as the XIAP IRES as depicted in Fig. 5. One of skill would have been motivated to do so to design antisense compounds that span the full range of the characterized IRES sequence to ensure hybridization given mRNA's secondary structure and the lack of accessibility for hybridizing molecules. Furthermore, it would have been obvious to incorporate said antisense molecules in vectors and/or in cells.

Moreover, it would be routine to incorporate such antisense molecules into vectors and subsequently introduce said vectors into cells to assess, for example, the antisense effects in cell culture. Given the skill at the time of invention and the knowledge in the art with respect to antisense technology, there would have been a reasonable expectation of success in modifying the antisense molecules of the '709 patent with what was then disclosed in the '709 patent's disclosure.

5. **Claims 69-77, 79-80, 82-87, 89-92, 94-95, 97, 104-120, 125-128 and 133 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 24 of U.S. Patent No. 6,171,821 B (hereinafter the '821 patent).**

This rejection is of record and repeated herein. The rejection is new in its administration to the new claims, which administration is necessitated by amendment. It is noted that Applicant requests this rejection be held in abeyance pending resolution of all other rejections. However, as other rejections are applied herein (i.e., the claims are not allowed), this rejection is maintained.

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 24 is drawn to an antisense molecule that targets the XIAP IRES and has at least 10 consecutive complementary nucleotides, with the target corresponding to SEQ ID Nos: 2 or 19-30. Therefore, both the reference claim 24 and the instant claims are directed to antisense molecules that are targeted to SEQ ID NO 2 (human XIAP IRES) and corresponding spans within the characterized IRES sequence (or SEQ ID NOs: 5, 7, 21, 25, 27 and 29) which are disclosed in the reference disclosure.

Therefore one of ordinary skill in examining claim 24 would have been motivated to examine the full disclosure to determine the full scope of the claimed invention and in so doing, the skilled artisan would be further motivated to modify the antisense molecules necessary to practice the invention of reference claim 24 to target the various portions of SEQ ID NO: 2, as claimed in the instant application, because by doing so one would obtain broader coverage of potential mRNA targets in the cell for antisense inhibition. Furthermore, it would have been obvious to incorporate said antisense molecules in vectors and/or in cells. Moreover, it would be routine to incorporate such antisense molecules into vectors and subsequently introduce said vectors into cells to assess, for example, the antisense effects in cell culture. Given the level of skill in the art at the time of invention, one of skill would have a reasonable expectation of success to design such antisense molecules based on the full disclosure of the '821 patent.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636